NEUROSECRETION

VI. A COMPARISON BETWEEN THE INTERCEREBRALIS–CARDIACUM–ALLATUM SYSTEM OF THE INSECTS AND THE HYPOTHALAMO–HYPOPHYSEAL SYSTEM OF THE VERTEBRATES [1]

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A comparison of data on the secretory activity of nerve cells in invertebrates with those obtained from corresponding studies in vertebrates revealed an interesting parallelism between the intercerebralis-cardiacum-allatum system of insects and the hypothalamo-hypophyseal system of vertebrates. The functional mechanism involved cannot be fully explained at present; but the observations are in themselves intriguing and offer a point of departure for the discussion of certain neuroendocrine relationships.

INSECTS

In the larvae of muscoid Diptera the ring-gland, an endocrine organ concerned with development (Hadorn, 1937; Hadorn and Neel, 1938; Burtt, 1938; Becker and Plagge, 1939; Vogt, 1942a; Gloor, 1943; Bodenstein, 1943a, 1943b, 1944), contains the elements of two glands, the corpus cardiacum and the corpus allatum (Scharrer and Hadorn, 1938; Vogt, 1942b; Day, 1943; Poulson, 1944). In other insects these two components form more or less individual organs. In *Leucophaea maderae,* a species used in the present study, the corpora cardiaca and allata are paired organs which, as in other representatives of the Orthoptera (De Lerma, 1937; Hanström, 1940), lie dorsal to the esophagus behind the brain. The anterior portions of the elongate corpora cardiaca form part of the wall of the dorsal blood vessel. The posterior ends of the corpora cardiaca are in contact with the corpora allata, which lie more laterally than the former. In Leucophaea the two glands are not, as in other species, separated by a nervus corporis allati but constitute an almost continuous mass of glandular tissue.

Histologically the corpus cardiacum can be easily differentiated from the corpus allatum. Cardiacum tissue contains nervous as well as glandular elements, whereas there is no indication of a nervous component in the corpus allatum. In Leucophaea the corpus cardiacum is to a varying degree filled with deeply staining colloid masses; in older specimens the gland may be replete with such acidophil substances. By comparison little material that can be interpreted as a secretory product is, as a rule, found in the corpus allatum. The physiological significance of the variations of the histological appearance of both the corpora cardiaca and corpora allata is not clear at present; but it is evident that they are both glands.

The corpora cardiaca receive a well defined fiber bundle (nervus corporis cardiaci, Pflugfelder, 1937; nervus corporis cardiaci I, Hanström, 1940; nervus occipitalis, Nesbitt, 1941) from the pars intercerebralis of the protocerebrum. In Leucophaea the fibers turn from their origin antero-medially and downward. Most of them, perhaps all, cross in the midline and continue toward the base of the brain. Thence the fiber bundle turns backward and shortly after leaving the brain enters the corpus cardiacum. The bundle can be followed all the way through the gland, which it innervates (Fig. 1). It seems that some of the fiber components enter the corpus allatum of the same side where they are distributed.
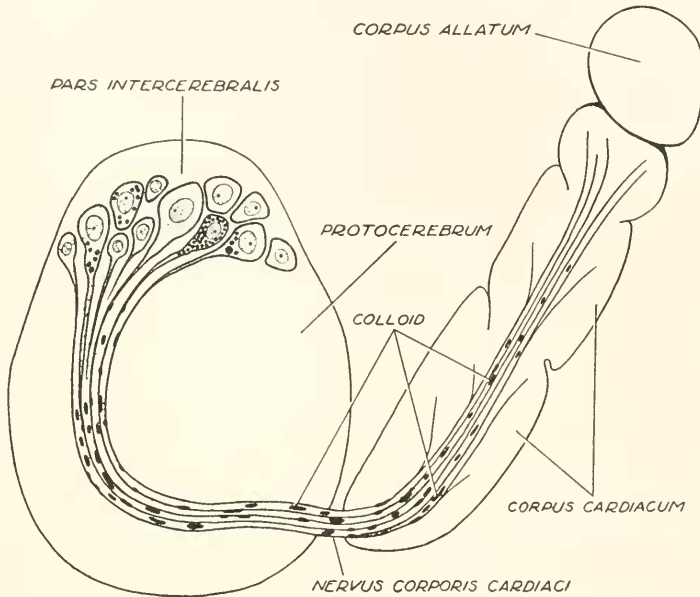

FIGURE 1. Diagram of the intercerebralis-cardiacum-allatum system of an insect.

The pars intercerebralis of the insect brain is distinguished by the occurrence of secreting nerve cells. Such cells have been found in Hymenoptera (Weyer, 1935; Scharrer, 1937), Hemiptera (Hanström, 1938; Wigglesworth, 1940), Lepidoptera (Day, 1940a), Coleoptera, Neuroptera, Trichoptera, and Diptera (Day, 1940b; Vogt, 1942a).[2] In the Orthopteran *Leucophaea maderae,* for instance, the medium sized nerve cells of the pars intercerebralis contain distinctly staining inclusions varying in size and number. There may be only two to three granules present in one cell, or they may be so numerous that they fill the entire cell body. Not only the number of granules in different cells, but also the number of secreting elements varies in different specimens. There may be numerous cells on either side of the midsagittal plane containing granules or there may be only a few such cells. The secretory material is in some cases concentrated near the axon hillock, and may continue for a certain distance into the axis cylinder, which in this case appears wider than in nerve cells of comparable size without secretory granules.

[2] R. P. Holdsworth found neurosecretory cells in the pars intercerebralis of Pteronarcys, a representative of the Plecoptera (personal communication).

The colloid granules in the pars intercerebralis resemble in size and stainability those found and previously described in the neurosecretory cells of the subesophageal ganglion (Scharrer, 1941a). The neuroglandular cells are larger in the subesophageal ganglion than in the pars intercerebralis.

Along the fibers of the nervus corporis cardiaci colloid masses are found in varying, sometimes very great amount, particularly in older specimens of Leucophaea. The colloid content of the fiber bundle permits its tracing and differentiation from other tracts (Fig. 1).

The concept of an anatomical system formed by the pars intercerebralis and the corpora cardiaca and allata facilitates the understanding of the hormonal regulation of postembryonic insect development. Several hormones derived from different sources have been demonstrated to control growth and differentiation in various groups of insects. The corpus allatum is known to furnish an "inhibitory hormone" in Hemiptera (Wigglesworth, 1934, 1936, 1940), Orthoptera (Pflugfelder, 1937; Pfeiffer, 1942; Scharrer, 1944), Lepidoptera (Bounhiol, 1939; Piepho, 1943), and Coleoptera (Radtke, quoted from Piepho, 1943). A substance originating in the brain brings about molting in Hemiptera (Wigglesworth, 1940), and pupation in Lepidoptera (Kopeć, 1922; Caspari and Plagge, 1935; Kühn and Piepho, 1936) and Hymenoptera (Schmieder, 1942). Additional centers in the thorax (or possibly upper abdomen) have been claimed to play a role in pupation and imaginal differentiation of Lepidoptera (Hachlow, 1932; Bounhiol, 1938; Bodenstein, 1938; Fukuda, 1940; Piepho, 1943) and Neuroptera (Ochsé, 1944). In the highly specialized muscoid Diptera the ring-gland containing both corpus cardiacum and allatum controls growth, molting (Bodenstein, 1944), pupation (Hadorn, 1937; Hadorn and Neel, 1938; Becker and Plagge, 1939; Vogt, 1942a), and imaginal differentiation (Bodenstein, 1943b), whereas the brain is said to have no influence on these processes. There is indirect evidence that at least the substance causing puparium formation is produced by the cardiacum component of the ring-gland (see Scharrer, 1941b). Finally, removal of the corpora cardiaca in Orthoptera causes a retardation of molting (Pfeiffer, 1939).

In an attempt to reconcile some of the seemingly divergent data it may be useful to discuss first the various hormones named, and second their source in the organism.

Concerning the hormones controlling postembryonic insect development two interpretations are possible: (a) Each developmental step is brought about by one or several specific hormones. Accordingly there would exist molting, pupation, and metamorphosis hormones. (b) There are two types of hormones interacting during development. The one type activates the imaginal potencies in a measure regulated by the responsiveness of the developing tissue and thus brings about periodic growth and differentiation. Factors of this type are called in this paper "growth and differentiation hormones." The other type, juvenile or inhibitory hormone, activates the "juvenile," i.e. larval potencies of the cells, and in this way prevents the onset of metamorphosis. According to this concept, first formulated by Wigglesworth (1934, 1936, 1940), the presence of both factors in adequate proportion causes larval (nymphal) molting, whereas in the absence of the juvenile factor metamorphosis takes place. There is strong evidence that this "dualistic" mode of regulation exists not only in hemimetabolous (Hemiptera, Wigglesworth, 1934, 1940; Orthoptera, Pflugfelder, 1937, 1940; Pfeiffer, 1942; Scharrer, 1944), but also in holo-

metabolous forms (Lepidoptera, Bounhiol, 1939; Coleoptera, Radtke, quoted from Piepho, 1943).

In holometabolous insects, then, the effect ascribed by certain authors to a "molting hormone" would actually result from the combined action of two hormonal factors, a juvenile hormone and a growth and differentiation hormone. Pupation and metamorphosis would take place in the presence of one or more differentiation factors alone.

As sources of the hormones controlling insect development three organs in the head region of insects are known at present: (1) the glandular corpora allata, (2) the corpora cardiaca, consisting of nervous and glandular elements, (3) the pars intercerebralis of the brain containing glandlike nerve cells.

In contrast to the known action of the corpus allatum which is the source of the juvenile hormone (see p. 244), the role of the two remaining centers has been less well understood. In one group of insects the brain seems to produce a hormone (or hormones) which in another group is provided by the corpus cardiacum. These two sources do not need to be treated as two separate centers of glandular activity, different as they may seem at first sight. On the basis of their unusual morphological relationship it is proposed to consider them as components of one neuro-endocrine complex whose role in the developing insect is the regulation of growth and differentiation.

As to the mechanism of this glandular complex there are two possibilities. Either both the brain and the corpus cardiacum cooperate in the elaboration of growth and differentiation factors, or in different animals the one or the other component has become the predominant hormone source. Considering the variability in the development of neuroglandular organs in the insect head one may expect to find examples for either alternative among the various groups of insects.

The first possibility has to be considered, if extirpation of one of the two glandular centers leads to disturbances but not to a complete interruption of the endocrine mechanism. For instance, it is known that cardiacectomy in Melanoplus (Orthoptera, Pfeiffer, 1939) delays but does not entirely prevent molting.

There are data that indicate the second possibility, i.e. an autonomous action of either the brain or the corpus cardiacum. In nymphs of Rhodnius (Hemiptera, Wigglesworth, 1940) brain implants cause molting in the absence of the corpus cardiacum. In Drosophila and Calliphora the ring-gland (in all probability its cardiacum component) furnishes growth and differentiation hormones, whereas the brain alone has little or no effect. Most of these data in Diptera (Hadorn, 1937; Hadorn and Neel, 1938; Burtt, 1938; Becker and Plagge, 1939; Vogt, 1942a; Gloor, 1943; Bodenstein, 1943a, 1943b, 1944), as well as observations made in other groups of insects, do not preclude, although they do not prove a collaboration between pars intercerebralis and corpus cardiacum in the production of growth and differentiation hormones.[3]

All these data and considerations concern the developing insect. In the adult the corpora allata control egg development (Wigglesworth, 1936; Pfeiffer, 1939; Thomsen, 1940; Vogt, 1940; Scharrer, 1943) and color change (Pflugfelder, 1939);

[3] Further information will be necessary about the identity and mode of action of certain thoracic centers, mentioned on p. 244, before they fit into the present concept of the hormonal control of insect development (see also Richards, 1937).

the functional significance of the intercerebralis-cardiacum complex is still unknown. However, the production of physiologically active substances by the intercerebralis-cardiacum complex also in the imago is indicated by the fact that extracts from either component in Periplaneta yield chromatophorotropic responses in crustaceans (Brown and Meglitsch, 1940).

In summary, the intercerebralis-cardiacum-allatum system furnishes two types of hormonal factors which by their interaction control the rate of insect development. The one type, i.e. growth and differentiation hormone (or hormones), originates in the neuroglandular intercerebralis-cardiacum complex, the other (juvenile, inhibitory hormone)in the corpus allatum. This seems to be the most satisfactory interpretation of the numerous existing observations. As has been indicated (p. 245) it is not the only one possible.

<div align="center">VERTEBRATES</div>

The pituitary gland consists of two components, the pars buccalis (anterior lobe), and the pars nervosa (posterior lobe). The latter receives its innervation from nuclei in the hypothalamus; how many of the nerve fibers also end in the anterior lobe, is not definitely known, and it seems to vary in different groups of vertebrates. In the fishes, the nucleus preopticus and the nucleus lateralis tuberis send their fibers to the hypophysis. The nucleus preopticus alone innervates the gland in the amphibians. In the reptiles the nucleus preopticus is divided into two nuclei, the nuclei supraopticus and paraventricularis (Meyer, 1935). The cells of these two nuclei send their axons to the pituitary gland in the reptiles and the mammals. The significance of these hypothalamic nuclei as nervous centers controlling pituitary activity has been studied carefully in some species such as the cat, particularly by Ranson and his collaborators (Ranson and Magoun, 1939).

The same cells which through their axons innervate part or all of the pituitary gland have been shown in a number of vertebrates to exhibit characteristics of gland cells (Scharrer and Scharrer, 1940). This means that the cells pass through cycles of secretory activity during which they produce granules and colloid droplets.

The question arises whether this secretory activity of the nerve cells is connected with the control of the pituitary gland or has no relation to this function. The latter would be difficult to understand. The nervous control of the neural lobe is known to be of great importance for the normal function of this organ. It seems inconceivable that the cells which innervate the gland could themselves change into gland cells to the extent observed in some animals if the secretory activity of these nerve cells would serve a purpose unrelated to the activity of the pituitary gland. Such an independent glandular function would probably interfere with the task of the cells of innervating the hypophysis.

The alternative, that the secretory activity of the neurons is part of the mechanism through which the hypothalamic nuclei exert control over the pituitary gland, would appear to be more acceptable. Evidence to support this view may be seen in two kinds of observations: (1) The secreted material can be traced along the axons to the hypophysis. (2) There is a seasonal cycle in certain cases of neurosecretory cells which may have a significance with regard to seasonal cycles in hypophyseal activity.

Granules and droplets, discharged by secreting nerve cells, have been traced along the axons in a number of species (Fig. 2). In the catfishes, *Noturus flavus* and *Ameiurus nebulosus*, the nucleus preopticus and the nucleus lateralis tuberis both consist of secreting nerve cells (Palay, 1943). Acidophil granules and droplets of the same kind as produced by these cells are found all along the fibers from the preoptic nucleus to the pituitary gland. This tract can actually be differentiated from other fiber connections by the granules which in Masson preparations stain red and mark the bundle as clearly as the black granules would in a successful Marchi preparation (Palay, unpublished).
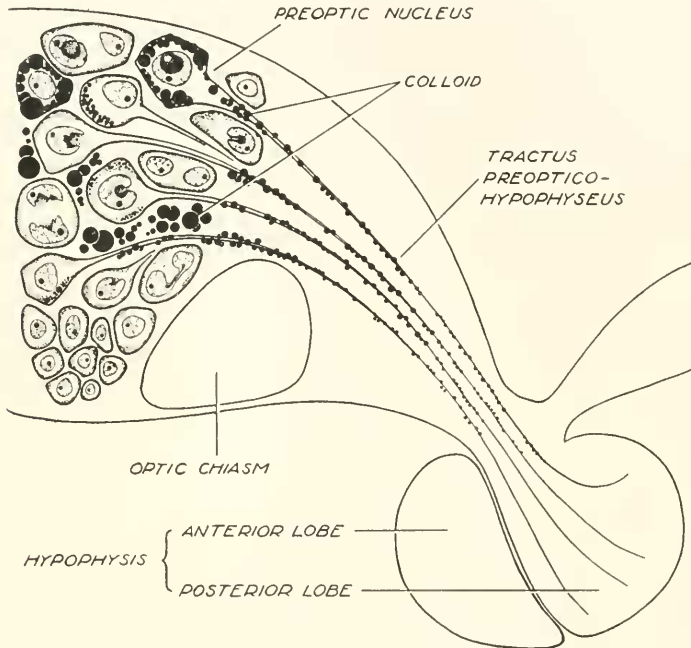
FIGURE 2. Diagram of the hypothalamo-hypophyseal system of a vertebrate.

The granules along the axons of the preoptic nucleus can be seen also in other fishes, such as Tinca (Scharrer, 1936), Fundulus, and Centropristes. Likewise in amphibians, for instance in the toad, the granules are attached to the axons in bead-like arrangement for a long distance from the cell of origin. In reptiles, particularly in snakes, the fiber tract between the supraoptic nucleus and the hypophysis may be filled with colloid droplets as in the catfish. Also in the human supraoptic nucleus cells have been seen with acidophil granules along the axon some distance from the cell body (Gaupp and Scharrer, 1935).

In the vertebrates a considerable amount of experimental work has been done, but the physiological role of the material secreted by the nerve cells is still unknown. All that can be said at present is that if the acidophil material discharged by the nerve cells contains an active principle, it appears to be directed toward the hypophysis.

It should be mentioned here that a number of investigators have suggested a migration in the opposite direction, i.e. of hypophyseal colloid from the pituitary gland to the hypothalamus (Edinger, 1911; Cushing, 1925; Collin, 1928; Popják, 1940). There is no doubt that this actually takes place. The hypophyseal colloid can be differentiated from the colloid of the nerve cells in that it stains slightly different and appears in the shape of irregular masses instead of sharply defined granules. This hypophyseal colloid cannot be traced very far, and it is questionable whether it reaches the hypothalamus; but the possibility that colloid may be exchanged in both directions must be acknowledged. The significance of such an exchange is largely obscure, but a close interrelation between the activity of the hypophysis and that of neurosecretory cells in the hypothalamus is suggested.

A seasonal cycle of the secretory activity of neurosecretory cells has been found so far only in one species of teleosts. The cells of the nucleus lateralis tuberis of the tench (*Tinca vulgaris*), a close relative of the carp, show no secretory activity during the winter months. It is very conspicuous during the summer months with gradual increase in spring and decrease in fall (Scharrer, 1936). In catfishes (*Ameiurus nebulosus* and *Noturus flavus*), collected during the past three years, no corresponding cycle was found (Scharrer and Palay, unpublished). The pituitary gland of fishes is also subject to seasonal changes (Bock, 1928; Matthews, 1939; Evans, 1940). Whether and in which way the cyclic hypophyseal phenomena are related to those taking place in the nucleus lateralis tuberis is not known at present. The data available require closer investigation.

Consequently it is proposed to follow the suggestion of physiologists and pathologists who have been considering the hypothalamic nuclei of higher animals together with the neural lobe as an interdependent system. Such a hypothalamo-hypophyseal system could be assumed to have originated from a hypothetical situation in which from one neuroglandular area in the brain the secreting hypothalamic nuclei and the pars nervosa of the hypophysis have been derived. The exchange of colloid, whatever its functional meaning may be, could be considered as a remnant of the original connection. Charlton (1932) has presented evidence that in phylogeny the nucleus preopticus of the fishes has migrated rostrally. The cauda of the nucleus preopticus in fact points toward the hypophysis, and the irregularly occurring nucleus lateralis tuberis is still in very close proximity to the pituitary gland.

DISCUSSION

A comparison of the hypothalamo-hypophyseal system of vertebrates with the intercerebralis-cardiacum-allatum system of insects reveals a parallelism which is the more striking because insect and vertebrate organs differ so greatly that no true organ homology can exist between these phyla.

The hypothalamic nuclei of the vertebrates have their equivalent in the pars intercerebralis of the insects. In both centers neurosecretory cells are found, and both send nerve fibers to innervate complex endocrine organs, i.e. the pituitary gland and the corpora cardiaca and allata. In both the vertebrates and the invertebrates these nerve fibers contain colloid which can be traced from the nerve cells all the way to the glands innervated by them.

The endocrine glands too are comparable as Hanström (1941) has pointed out. The hypophysis produces a number of well-known hormones influencing growth,

gonadal development, chromatophores, etc. The corpora cardiaca and allata control processes of equivalent importance in the life of insects, such as growth and metamorphosis, egg development, color change, etc. Evidently the corpora cardiaca and allata play a role in insects similar to that of the pituitary gland in vertebrates.

Both glands are composite structures. The pituitary consists of a neural portion which forms the posterior lobe, and a glandular portion which forms the anterior lobe. These two components become associated to a varying extent; they are most closely connected in the teleosts where the pars nervosa penetrates the pars glandularis. In the insects the corpora cardiaca are comparable to the neural portion, the corpora allata to the glandular portion of the hypophysis. The corpora cardiaca and allata become associated in most insects; in the muscoid Diptera they form an organ (ring-gland) in which the two components can be differentiated only histologically (Scharrer and Hadorn, 1938; Vogt, 1942b; Day, 1943; Poulson, 1944).

The parallelism in the organization of the two systems here compared could be merely a coincidence. However, it seems more likely that the comparison is significant in that it indicates a fundamentally similar relationship between the "master glands" and the central nervous system in invertebrates and vertebrates.

Summary

The hypothalamo-hypophyseal system in vertebrates is in many respects similar to the intercerebralis-cardiacum-allatum system in insects.

(1) In vertebrates the hypothalamic nuclei innervating the pars nervosa of the pituitary gland contain secreting nerve cells. In a number of species colloid droplets can be traced along the axons from the neurosecretory cells of the hypothalamus to the hypophysis.

(2) In insects the pars intercerebralis of the protocerebrum contains neurosecretory cells. A bundle (nervus corporis cardiaci) innervating the corpus cardiacum and probably also the corpus allatum originates in the pars intercerebralis. In Leucophaea (Orthoptera) as in the vertebrates, colloid can be traced from the secreting nerve cells of the pars intercerebralis to the corpora cardiaca all along the nervus corporis cardiaci.

(3) On the basis of these morphological relationships the hypothalamic nuclei (nucleus preopticus and its homologues) and the pars nervosa of the hypophysis appear as one closely interconnected system. Likewise the pars intercerebralis and the corpus cardiacum of insects may be viewed as one neuro-endocrine complex rather than as two separate sources of hormones. In this way certain seemingly inconsistent data concerning the endocrine control of development in insects can be better understood (see p. 244).

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